WORKPLAN FOR RISK EVALUATION OF DODECYLBENZENE USING QUANTITATIVE STRUCTURE-ACTIVITY RELATIONSHIPS

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MAIN FACILITY, 9300 RAYO AVENUE
SOUTHGATE, CALIFORNIA

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The material and data in this report were prepared under the supervision and direction of the undersigned.

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1 INTRODUCTION

A health risk assessment (HRA) was previously performed by EMCON for dodecylbenzene (DDB) in soil at the former Dial Corp (Dial) main facility at 9300 Rayo Avenue, South Gate, California (EMCON, 1994). In the HRA, it was concluded that levels of DDB which had been detected in site soil did not pose an unacceptable health risk for potentially exposed receptors (on-site workers). The California Regional Water Quality Control Board, Los Angeles Region (RWQCB) provided comments relating to the reference dose developed by EMCON and fate and transport properties of DDB used in the HRA (RWQCB, 1996). Because toxicity and fate and transport parameter values for DDB were not available, data from Monsanto for partially characterized mixtures of alkylbenzenes were used to supply the toxicological and transport parameters for assessing exposures and risks in the HRA. In their comments, the RWQCB requested that a quantitative uncertainty analysis be performed on the reference dose and transport parameters used for DDB to assess the confidence in the conclusions reached in the HRA.

Because additional information on DDB or alkylate mixtures is not available, implementing the comments provided by the RWQCB is not practical, as no additional insight can be provided using their recommended approach. A meeting was held on May 8, 1996 involving the RWQCB, Dial, and EMCON to discuss an alternative approach to addressing the RWQCB concerns. This alternate approach uses information on discrete chemicals rather than on partially characterized mixtures. Data on discrete chemicals structurally related to DDB can be used to estimate values for DDB via a quantitative structure-activity relationship (QSAR) method. This method would allow development of a reference dose (RfD) used to evaluate noncarcinogenic toxicity and transport parameters for DDB that can be compared with values used in the HRA. Information already compiled in the HRA regarding the likely carcinogenic potential of DDB indicates that it does not act as a possible or probable human carcinogen (EMCON, 1994). Therefore, no further effort will be made to characterize the carcinogenic potential of this chemical. This QSAR approach provides a technically defensible way to evaluate the appropriateness of the values used in the HRA. As stated in USEPA's revised proposed guidelines for carcinogen risk assessment (USEPA, 1996b), the predictive capability of QSAR has been documented.

It was recommended during the meeting that a workplan be prepared to allow the RWQCB to fully review the QSAR approach prior to its implementation. This document is intended to meet that recommendation. Once the workplan is approved and

implemented, methods, inputs, and results of the QSAR approach, and impacts on risk estimates would be provided as an appendix to the original HRA. The approach used to develop an alternate RfD for DDB is presented below, followed by the approach to be used for developing alternate chemical-specific transport parameters; additional site data will be gathered for site-specific transport parameters.

2 QSAR TOXICITY APPROACH

The concept behind the QSAR approach, is that structurally similar compounds have similar mechanisms of action (USEPA, 1996b; Faustman and Omenn, 1996). If toxicological information is available on some compounds in a group, it can be extrapolated to other chemicals in the group. A chemical's structure, solubility, stability, pH sensitivity, electrophilicity, and chemical reactivity can provide important information for use in hazard identification and risk assessment. This approach has been used by USEPA and California to develop toxicity equivalence factors (TEFs) for dioxins (USEPA, 1994) and polycyclic aromatic hydrocarbons (PAHs; USEPA, 1993). The approach is also used in response to premanufacturing notices for new chemicals manufactured under the Toxic Substances Control Act (TSCA; Faustman and Omenn, 1996). Information that is useful for conducting a QSAR analysis includes:

- Nature and reactivity of physiologically active portion of a chemical
- Mechanism of toxic action
- Physicochemical properties
- Structural and substructural features (e.g., stearic hindrance)
- Metabolic pathway (e.g., activation:detoxification ratio)
- Exposure route.

The QSAR approach is most appropriate for chemicals that are similar regarding these properties. For example, the QSAR approach is effective for estimating the toxicity of a chemical if the chemicals used in the analysis have similar chemical structures, mechanisms of action, physiochemical properties, and metabolic pathways to that of the target compound. Because DDB (C_6H_6 - $[CH_2]_{11}$ - CH_3) is in the same chemical class as toluene (C_6H_6 - CH_3), ethylbenzene (C_6H_6 - CH_2 - CH_3), and other chemicals with similar structures and mechanisms of action for noncancer effects, this approach is relevant to the present study.

2.1 General Approach

Due to the lack of available toxicity data for DDB (EMCON, 1994), a QSAR approach based on data for various alkylbenzenes will be used to estimate an oral reference dose (RfD) for DDB. Although the most relevant route of current exposure to DDB at the site is via inhalation, direct contact will also be possible once the asphalt is removed from the site. Available data on both inhalation and ingestion (i.e., oral) exposure routes will be compiled, but is likely that oral toxicity studies will predominate in the literature. Because data for different chemicals on the same exposure route is needed to conduct QSAR, it is likely that the RfD developed using this approach will be most relevant for oral exposure. In the absence of sufficient information on the inhalation route, this oral RfD will also be used to approximate an inhalation RfD, consistent with Cal-EPA guidance (i.e., route-to-route extrapolation).

Oral rat LD_{50} data will be compiled for various alkylbenzenes for which this information is available. Based upon a preliminary review of the literature, data are available for toluene, ethylbenzene, propylbenzene (C_6H_6 - $[CH_2]_2$ - CH_3), and butylbenzene (C_6H_6 - $[CH_2]_3$ - CH_3). These chemicals represent benzene with 1-, 2-, 3-, and 4-carbon straight chain alkyl groups attached, respectively. A "best fit" equation will then be developed for the relationship between structure (i.e., the effect of additional CH_2 units) and LD_{50} toxicity. This relationship will be used to estimate an LD_{50} value for DDB. One study on DDB (an oral rat study) is available (Clayton and Clayton, 1982, as cited in HSDB, 1996). This study indicated that no deaths were reported at 5,000 milligrams per kilogram (mg/kg), the highest concentration applied. This DDB study will be used to verify the appropriateness of the estimated LD_{50} value for DDB using the QSAR approach.

The estimated LD_{50} will then be converted to a no-observed effect level (NOEL) using information relating LD_{50} values and NOELs from Layton et al. (1987) and Lewis et al. (1990). This estimated NOEL may then be modified using other toxicity data on non-lethal endpoints available for specific alkylbenzenes. Once a NOEL has been fully developed for DDB, USEPA uncertainty factors (USEPA, 1989) and metabolic scaling factors (USEPA, 1996) will be applied to convert this rat-based NOEL to a human-equivalent RfD.

A literature search will also be performed to locate the relevant LD_{50} toxicity studies which will be used as the basis for a RfD for DDB. A combination of information sources already in house with other on-line sources will be used to obtain the LD_{50} data. Sources already in hand include:

- Sax's Dangerous Properties of Industrial Materials (Lewis, 1992)
- Handbook of Environmental Data on Organic Chemicals (Verschueren, 1983)

- The Merck Index (Merck, 1989)
- Integrated Risk Information Service (IRIS; USEPA, 1996a)
- Registry of Toxic Environmental Chemical Substances (RTECS, 1996)
- Hazardous Substances Databank (HSDB, 1996)

Information from the latter three databases has been compiled for toluene, ethylbenzene, propylbenzene, and butylbenzene. In addition to these sources, EMCON will make use of its internet connection to identify additional information relevant to this work.

2.2 Lethal Toxicity Data for Alkylbenzenes

Information on oral rat LD_{50} values for alkylbenzenes ranging between one and fifteen alkyl groups in length (DDB contains a 12-carbon alkyl chain) will be used to develop a toxicity value for DDB. Based on preliminary review, a substantial amount of information is available for toluene, ethylbenzene, propylbenzene, and butylbenzene. Other data may exist for the higher homologs (e.g., chemicals with the same basic structure and different numbers of repeating methylene units). If so, these additional studies will be obtained and used for the higher homologs. Each LD_{50} study obtained from the literature will be summarized in tabular format in the Appendix to the HRA. Additionally, available information pertaining to uncertainties associated with a particular study will be discussed in the text.

On the basis of preliminary information, it appears that the lethal toxicity of the different alkylbenzenes is similar. LD_{50} values for the four homologs from toluene to butylbenzene range by less than a factor of 2; in general the lethality decreases as the length of the alkyl chain increases. Differential toxicity between benzene (no alkyl groups) and toluene (one alkyl group) is substantial. Addition of an alkyl group to the benzene ring results in a substantial reduction of noncancer potency, and apparently eliminates the cancer effects of benzene. Once an alkyl group is present on the benzene ring, toxicity appears to be relatively unaffected by the addition of additional CH_2 groups onto the alkyl chain. Based on the available data for the four homologs, decrease in toxicity with increasing alkyl chain length appears to be sublinear. Because of this, it is likely that values for the longer-chained homologs will be similar to, but less than, those for the shorter-chained homologs. This follows from the known metabolic mechanism for these types of chemicals, which involves oxidation of the alkyl bonds on the side chain. Because this metabolism can occur at any of the alkyl groups on the side chain and occurs quickly, toxicologically these homologs represent very similar chemicals. It is possible that, for a sufficiently long side chain, the physical size of the molecule may have a substantial impact on toxicity. Unless this can be documented via the literature, it appears the potency of alkylbenzenes is not appreciably affected by the length of the alkyl chain.

2.3 Conversion of Lethal Value to NOEL

Lewis et al. (1990) evaluated species- and chemical-specific ratios between LD_{50} values and NOELs in a total of 490 studies. This comparison provides an evaluation of the relationship between a NOEL and an LD_{50} for use in developing an appropriate uncertainty factor to extrapolate from an LD_{50} to a NOEL. On the basis of the results obtained by Lewis et al. (1990), lowering the LD_{50} by a factor of 6 appears to be sufficiently protective for individuals within the population, including sensitive individuals. Because LD_{50} data are based on acute studies, the NOEL extrapolated from such data should be considered to be a short-term (e.g., acute) NOEL. The acute NOEL will then be adjusted to an equivalent chronic NOEL using an appropriate uncertainty factor. Although USEPA uses a value of 10 for this adjustment, information provided in Lewis et al. (1990) indicates a value of 5 is sufficient. Therefore, a range of uncertainty factors between 30 (5 x 6) and 60 (10 x 6) can be used to adjust an LD_{50} value to an equivalent chronic NOEL. This is consistent with the data provided by Layton et al. (1987), who calculated a geometric ratio between chronic rat NOELs and LD_{50} values of 66. To be conservative, the USEPA factor of 10 will be used to adjust the acute NOEL to a chronic NOEL, resulting in a total uncertainty factor of 60 to adjust the LD_{50} to a chronic NOEL.

The chronic NOEL will then be further adjusted to an RfD by incorporating an uncertainty factor of 10 to account for extrapolation across species (i.e., from rats to humans). A modifying factor ranging from 1 to 10 will also be applied depending on the amount and quality of data available. In an effort to use a weight-of-evidence approach to identifying an appropriate RfD, the resulting RfD value using the above approach may be adjusted depending on the available data on chronic NOELs for alkylbenzenes. Any deviations from this approach used in the analysis will be documented and justified in the Appendix.

3 TRANSPORT OF DODECYLBENZENE

In their comment letter, the RWQCB recommended that chemical-specific input parameters used in the SESOIL leachate model conducted in the HRA be modified to include DDB-specific inputs, and that SESOIL parameters describing properties of the vadose zone, the hydrologic cycle, and the aquifer also be based on measured, site-specific values (RWQCB, 1996). The RWQCB also recommended that volatilization modeling be performed in addition to the pathways evaluated in the HRA. Based on these comments, two transport processes will be evaluated for DDB: 1) leachability from soil, and 2) volatilization from soil. Due to the lack of literature transport values for DDB, chemical-specific inputs for both leaching and volatilization modeling will be estimated using a QSAR approach similar to the method described in Section 2.1 (toxicity).

3.1 General Approach

A QSAR approach will be used to refine parameters necessary to conduct transport modeling of DDB for use in estimating exposures and risks. As previously discussed, physicochemical properties are important parameters for QSAR studies. Therefore, incorporation of this approach into the overall project plan will also assist in identifying the appropriate toxicity value for DDB. To identify appropriate parameter values on leachability and volatilization, a literature search combining information sources already in house with on-line sources will be performed. Those sources already in hand include:

- USEPA Region IX Preliminary Remediation Goals (USEPA, 1995)
- Illustrated Handbook of Physical-Chemical Properties and Environmental Fate for Organic Chemicals, Vol. 1 (Mackay et al., 1993).
- Handbook of Environmental Data on Organic Chemicals (Verschueren, 1983)
- Registry of Toxic Environmental Chemical Substances (RTECS, 1996)
- Hazardous Substances Databank (HSDB, 1996)

Information from the latter two databases has been compiled for toluene, ethylbenzene, propylbenzene, and butylbenzene. In addition to these sources, EMCON will make use of its internet connection to identify additional information relevant to this work.

3.2 Leachate Modeling

There are five chemical-specific inputs used in the SESOIL model:

- Water solubility
- Soil sorption coefficient
- Henry's Law constant
- Air diffusion coefficient
- Molecular weight.

Values for the first three parameters will be estimated using the following methods. Values for both water solubility and soil sorption coefficient for alkylbenzenes will compiled from the available literature. In cases where only one of these two parameters is listed, empirically derived regression relationships will be used to estimate one of these two parameters from knowledge of the other. Lyman et al. (1990) contains an extensive listing and description of these regression relationships. Because each of these relationships is developed using different types of chemicals, it is important to select an equation that has been developed based on chemicals expected to behave similarly to alkylbenzenes. With this in mind, the method of Karickhoff et al. (1979) is the most appropriate regression equation for alkylbenzene compounds (Lyman et al. 1990) and will be used in this evaluation. The Henry's Law constant for each alkylbenzene will be obtained directly from the literature, if available. If not available, vapor pressures of the alkylbenzenes will be compiled from the literature and used to estimate the vapor pressure of DDB by dividing the vapor pressure (in atmospheres) by the water solubility (in moles per cubic meter). Once water solubility, soil sorption coefficient, and Henry's constant data are compiled for those alkylbenzenes for which sufficient information is available from the literature, three best-fit relationships will be developed (i.e., effects of additional CH_2 units) based on this data to allow the estimation of values for these three parameters for DDB itself.

The air diffusion coefficient will be estimated for DDB directly by using a structure-based relationship developed by Fuller, described by Perry and Chilton (1973), and recommended by EPA (USEPA, 1988). This method relies on estimating a chemical's LeBas molar volume by adding individual volume contributions from atoms and atom types present in the structure. This method is widely used for a large variety of organic chemicals.

The molecular weight of DDB is a known value and was previously used in the HRA. This same value will be used for the QSAR approach.

Site-specific input parameters needed for leachate modeling (i.e., soil bulk density, total organic carbon [TOC], vertical permeability, and soil moisture content) will be obtained from field and laboratory measurements and analysis of additional soil samples to be collected from the site.

3.3 Volatilization Modeling

Because some detected subsurface soil concentrations of DDB are greater than 10,000 mg/kg, it was assumed that DDB may be present at levels exceeding its soil saturation limit. This assumption has a significant impact on selecting an appropriate soil volatilization model. Having assumed that DDB concentrations are greater than saturation limits, a Raoults Law-based volatilization model is more appropriate than a Henrys Law-based approach. Therefore, Shen's model (Shen, 1981) will be used to estimate a vapor flux of DDB at the soil surface. This model has been recommended by EPA (USEPA, 1988). To evaluate potential future exposures, it will be assumed that the current asphalt cover will be removed and no surface barriers to volatilization are present. A value of 2.5 feet will be conservatively used as the thickness of clean soil cover at the site, based on available site data which show detectable concentrations no shallower than about five feet bgs.

Only two chemical-specific inputs are required for this model: (1) vapor pressure and (2) soil concentration of DDB. Vapor pressure data will be obtained for the alkylbenzenes and used in a structure-activity calculation to estimate a vapor pressure value for DDB. Some of the necessary vapor pressure data may be collected as part of developing the Henrys Law constant for DDB (Section 3.1.1). A value of 12,660 mg/kg, corresponding to the 95 percent upper confidence limit of the arithmetic mean (95UCL) of the soil data, will be used as a soil source concentration. This is the same source concentration used in the HRA to estimate exposures from direct contact and dust inhalation.

The DDB vapor flux estimated using Shen's model will be input into the same box model used in the HRA to estimate outdoor air concentrations of DDB for use in the dose and risk estimates.

4 SUMMARY

A health risk assessment was previously performed by EMCON for DDB in soil, which concluded that levels of DDB which had been detected at the site did not pose an unacceptable health risk for on-site workers. Agency comments on the HRA focused on the uncertainties associated with using toxicity and fate and transport data from alkylate mixtures, as data for DDB itself are unavailable. A quantitative uncertainty analysis was initially proposed, but EMCON argued that such an approach would be impractical, due to the lack of sufficient information on such alkylate mixtures. As an alternative to an uncertainty analysis, EMCON proposed that a QSAR approach be used, based on available data for homologs of DDB.

A QSAR approach is described for both the refinement of the toxicological data for DDB, and for revised transport modeling. A QSAR approach is supported by recent EPA guidelines, and is applicable to DDB because of the availability of data for homologous chemicals. The QSAR approach will be based on the compilation of toxicity and transport data for alkylbenzene compounds. Data are available for toluene, ethylbenzene, propylbenzene, and butylbenzene; a literature search for data for other longer-chained alkylbenzene homologs will be performed. These chemicals represent benzene with 1-, 2-, 3-, 4- or longer-carbon straight chain alkyl groups attached, respectively. A "best fit" equation will be developed for the relationship between structure (i.e., the effect of additional CH_2 units) and LD_{50} toxicity. This relationship will be used to estimate an LD_{50} value for DDB.

The refined toxicity and transport properties will then be used in the exposure assessment and risk characterization portions of the HRA to estimate non-carcinogenic health hazards for potential exposure to DDB. The refined input, methods, and results will be presented in an appendix to the original HRA.

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